Environmental Health Perspectives
Vol. 40, pp. 107-120, 1981

Role of Cadmium in Carcinogenesis with Special Reference to Cancer of the Prostate

by Magnus Piscator*

It has been shown in animal experiments that injections of large amounts of cadmium cause sarcoma at injection sites or testicular damage and eventually testicular tumors. Long-term exposure with small doses of cadmium has not caused testicular or prostatic tumors in experimental animals.

Epidemiological studies on cadmium-exposed workers have shown excess deaths due to prostatic cancer in at least three independent investigations. All reported cases probably had considerable exposure decades ago, but there are not enough data to permit any dose-response calculations. The general epidemiology of prostatic cancer was not taken into account in any of the studies. A review of recent literature on epidemiology of prostatic cancer has revealed some basic facts. Small latent prostatic cancer has been shown to be as common in areas with low mortality from prostatic cancer as in areas with high mortality. In the U.S. the black population has a much higher death rate from prostatic cancer than the white population. Marital status has also been implied as a factor in the development of prostatic cancer. Black populations in Africa have much lower death rates than blacks in the U.S., which may depend on large differences in dietary habits. Thus racial, sexual and nutritional factors might be important for the development of prostatic cancer, since they may influence hormonal status. Cadmium concentrations in testes and prostate increase during heavy exposure, and it has been shown that testosterone synthesis will decrease in cadmium-exposed animals. Excessive exposure may interfere with the zinc/hormone relationship in the prostate, which could be a possible explanation for the development of prostatic cancer in heavily exposed individuals. Direct action of cadmium on the cells is not likely, nor is it probable that low level exposure to cadmium can be a causative factor for prostatic cancer.

Introduction

The increasing pollution by cadmium and its present and future influence on human health has attracted great interest during the last decade. A large number of reviews have appeared (*1-10*). The effects of long-term low level exposure via air or from ingestion of contaminated food have been studied in many countries, and it is now well established that the kidney is the critical organ with respect to systemic effects. It has been estimated that a cadmium concentration of about 200 mg/kg wet weight in renal cortex might cause tubular dysfunction. Minor controversies still exist about the renal effects, both regarding critical concentration and certain diagnostic procedures. However, the possible relationship between cadmium exposure and cancer is far more controversial. In 1974, it was concluded by Friberg, et al. (*1*): "The carcinogenic evidence of cadmium in human beings is by no means conclusive, but fully motivates further intensified studies in groups exposed industrially, as well as from food and ambient air." There were at the time a number of reports (*11-22*) on the experimental induction of cancer in animals at injection sites or in the testes after cadmium doses which induced severe testicular damage. Concerning humans, there were a few reports on

*Department of Environmental Hygiene, Karolinska Institute, and the National Institute of Environmental Medicine, S-104 01 Stockholm, Sweden.

mortality in cadmium exposed workers (*23-25*). In one study an increased incidence of cancer of the prostate was reported (*23*).

More experimental long-term studies have since been performed (*26-28*), as well as a few studies on cancer mortality in human beings with verified or suspected exposure to cadmium (*29-31*). One particular study on mortality of cadmium workers (*29*) led IARC (*32*) to the following conclusion: "Available studies indicate that occupational exposure to cadmium in some form (possibly the oxide) increases the risk of prostate cancer in man. In addition, one of these studies suggests an increased risk of respiratory tract cancer." After this statement by IARC, data from one more study have indicated that workers exposed to cadmium might have an increased risk of developing cancer of the prostate (*33*).

The following will focus on the possible relationship between cadmium and cancer of the prostate. However, it has been deemed necessary to examine in more detail the epidemiology of cancer of the prostate and also the physiology and biochemistry of the prostate gland. These facts should be combined with what is known about metabolism and toxicity of cadmium and cadmium/zinc relationships in the body. In most papers concerned with the relationship between cancer of the prostate and cadmium, these factors have not been taken into account.

Cadmium

Exposure, Metabolism and Systemic Effects of Cadmium

Recent data show that the intake of cadmium via food is less than estimated earlier. Results from a cooperative study in Japan, U.S.A and Sweden, showed that whereas the daily intake was about 20 μg on an average in the U.S. and Sweden, it was more than twice as high in Japan (*34*). Other studies indicate as well that the intake is about 20 μg in West European countries and the U.S. (*35*). There may be large individual variation due to dietary habits. Absorption will be influenced by the presence of other substances in the diet, e.g., calcium and iron (*1, 36*) and by deficiency states. Exposure via ambient air is in most cases low, since cadmium concentrations in rural areas are about 1 ng/m^3 or less, and in urban areas without major cadmium-emitting industries, the average concentrations are generally less than 10 ng/m^3. Average concentrations in air near cadmium emitting industries may be between 0.1 and 0.5 μg/m^3. The inhaled amount of cadmium within 500 m of such point sources may be a few micrograms (*1, 35*). Concentrations in working environments may vary from a few micrograms per cubic meter to several milligrams per cubic meter. In many industries exposure is much less today compared to exposure 10 to 30 years ago (*37*). This is important to keep in mind when discussing carcinogenic effects. Also important for evaluating respiratory exposure are particle size and type of compound. Particles formed from cadmium oxide fume are small and deposited mainly in the lower part of the respiratory tract and the alveoli. They are relatively easily absorbed, whereas large particles of, e.g., cadmium sulfide, to a large extent deposited in the upper respiratory tract, have a relatively low solubility and absorption. Clearance of particles from the respiratory tract to the gastrointestinal tract must also be taken into account. Another factor complicating the evaluation of respiratory exposure in industrial workers is the secondary exposure which might occur from smoking contaminated cigarettes or pipe tobacco. Considerable oral exposure may occur from contact with deposited dust. Examples of that type of exposure have recently been given (*38*). For nonsmoking members of the general population intake via food is the most important. It has been estimated (*1*) that a smoker may inhale a few micrograms of cadmium every day due to the presence of cadmium in tobacco. Several studies have shown that smokers have considerably higher renal concentrations of cadmium than non-smokers of the same age (*1, 39*).

Cadmium absorbed from the lungs or the gut (*1*) is initially stored in the liver, where practically all cadmium will be bound to the metal-binding protein metallothionein. Information about the protein and its importance for the metabolism of zinc, copper and cadmium is given in a recent book (*40*) and a recent conference report (*41*). Cadmium is slowly released from the liver and it eventually appears in the kidneys. Since metallothionein is a low molecular weight protein, it is conceivable that it is filtered through the glomeruli and then reabsorbed in the proximal part of the renal tubules. Only a minor part of cadmium in serum appears to be bound to metallothionein. However, a metallothionein concentration in plasma of less than 100 ng/l. would be sufficient to explain the normal accumulation of cadmium in human kidneys. Cadmium disappears very slowly from the kidneys as well, and it has been estimated (*1*) that the half-life for cadmium in the human body may be up to 30 years. In the above-mentioned cooperative study (*34*) it was found that among adult human beings in the U.S. and Sweden, the renal cortex concentrations of cadmium on an average were about 20 mg/kg wet

weight, whereas in Japan the concentrations in a nonpolluted area were 2-3 times higher. Urinary concentrations of cadmium were below 1 μg/l. in U.S.A. and Sweden, whereas in Japan they were close to 2 μg/l.

Respiratory symptoms were common among industrial workers exposed earlier to high cadmium concentrations but present exposure in most industries seems to be below levels which may cause pronounced symptoms. The main interest has been focused on renal effects. It has been repeatedly shown in studies on industrial workers (*1*, *42-45*) as well as the general population (*46*) that excessive exposure to cadmium can cause renal tubular dysfunction. The first sign of this tubular dysfunction is the excretion of low molecular weight serum proteins (*47*, *48*). Increased excretion of such proteins, e.g., β_2-microglobulin and retinol-binding proteins, is thought to be due to a decrease in the reabsorption in the tubules of these proteins. As mentioned in the introduction, such effects may occur at concentrations around 200 mg/kg wet weight in renal cortex.

Demonstration of an increased excretion of such proteins in urine is thus at present the best method for diagnosis of early effects of cadmium (*49*, *50*). In more advanced cases of cadmium poisoning, excretion of glucose, amino acids, phosphorus and calcium may also be increased (*1*, *44*, *47*). The disturbed mineral metabolism may lead to renal stones, as seen in male Swedish workers (*1*, *42*), or osteomalacia, so called Itai-Itai disease, seen in Japanese women (*1*). Studies on industrially exposed men have shown that renal damage may appear later after exposure has ceased. This is due to the transfer of cadmium from liver to kidneys; after a few years, however, there will be no further progress, nor regress, of the disease (*49*).

Concerning long-term effects on other organs, the endocrine glands are of special interest when discussing cadmium and the prostate. Berlin and Ullberg (*51*) found in their studies on distribution of injected cadmium in mice that the metal accumulated in the pituitary gland. Zielenska-Psuja et al. (*52*) gave rats oral doses of about 5.4 and 54 mg Cd/kg body weight for periods of 3 to 15 months. It was found that the lower dose level caused an increase of serum LH concentrations during the first 12 months of exposure, compared to controls. However, after 15 months the exposed animals had lower LH concentrations than the controls. A higher dose level caused increased LH during the first 6 months, but after 12 months concentrations were lower than in controls. During the first 3 months a dose-dependent reduction in serum levels of testosterone was noted. Thereafter testosterone levels were higher in the exposed than in controls. Testes weights increased during the first part of the study in both exposure groups, but were reduced in the high exposure group after 12 months. In a large number of studies it has been shown that injection of several milligrams of cadmium/kg body weight to animals causes acute testicular necrosis and, as a late sequela, even testicular cancer (*1*, *53*). There are only a few reports on testicular effects of long-term administration of cadmium to experimental animals. Piscator and Axelsson (*54*) and Nordberg (*55*) did not find any histological changes in testes of rabbits or mice given subcutaneous injections of 0.25 mg/kg 5 days a week for 6 months. However, Nordberg and Piscator (*56*) found a decrease in protein excretion in cadmium exposed mice before renal damage had appeared, possibly caused by decreased testosterone production of the interstitial cells in the testes. Nordberg (*57*) found in mice exposed to subcutaneous injections of 0.25 mg Cd/kg 5 days a week for 6 months that there were changes in the seminal vesicles consistent with decreased testosterone levels. In the above mentioned work by Zielenska-Psuja et al. (*52*), histological changes in the testes were not seen after 3 or 6 months exposure. Assuming 1% absorption, the doses given should correspond to absorbed amounts of 0.05 or 0.50 mg/kg body weight. After 12 or 15 months of exposure a dose-dependent effect on the testicles was seen with a high proportion of damaged seminiferous tubules in the high exposure group. (In the paper it is stated that determination of cadmium has been performed on the testes and that such data are found in Table 3. However, no such table is found in the paper). As mentioned earlier, there was a significant dose-dependent decrease in serium testosterone levels during the first 3 months of the study. However, further exposure caused increases in serum testosterone. Thus, after 15 months the testosterone level was about twice as high in the low exposure group as in controls, whereas the high exposure group had the same concentrations as the control group. In rats given cadmium in drinking water at a concentration of 34.4 mg/l. for 6 weeks, with low and adequate intakes of zinc, it was found that the *in vitro* synthesis of testosterone from progesterone was more reduced in the cadmium-exposed group with low intake of zinc, compared to groups either on a low zinc intake or exposed to cadmium with an adequate supply of zinc (*58*).

With regard to human beings, it was reported by Smith et al. (*59*) that autopsies of men occupationally exposed to cadmium revealed increased concentrations of cadmium in prostate and testicles. Excretion of androgens in urine of cadmium work-

ers was studied by Favino et al. (*60*). Ten workers exposed to cadmium were compared to 10 controls matched for age. There was no difference between exposed and controls with regard to excretion of total 17-ketosteroids, androsterone, etiocholanolone and testosterone. There was a tendency for a decrease in the excretion of epitestosterone among the exposed subjects.

Experimental Carcinogenicity of Cadmium

Sarcomata at injection sites have been induced in rats after subcutaneous or intramuscular injections of cadmium in the form of metal powder, sulfide, chloride, sulfate or in ferritin contaminated with large amounts of cadmium (*11-17*). The doses given were large and in some of these studies it was also found that after initial testicular damage tumors developed in the testes (*11, 13-15*). It has also been shown that lower doses, not capable of causing testicular necrosis, would induce sarcomata at the injection sites after subcutaneous or intramuscular injection (*18*).

In contrast to the dramatic results of injection studies, long-term studies with mice or rats given cadmium in drinking water at a concentration of 5 mg/1. did not give any consistent results. More tumors appeared among cadmium exposed rats, while the opposite was found among cadmium exposed mice, as compared to controls (*19-21*).

In a recent study (*28*), groups of 50 male or female rats were given cadmium in drinking water at concentrations of 3, 10, and 50 mg/1. for two years. No prostatic tumors were found. There was no difference between exposed animals and controls with regard to malignant tumors in other organs. Data on cadmium concentrations in organs were not given.

Three studies, especially designed to investigate the connection between cadmium exposure and cancer of the prostate have been reported (*22, 26, 27*). In the first study by Levy et al. (*22*) rats were given weekly subcutaneous injections of cadmium sulfate in doses of 0.22, 0.44, and 0.87 mg Cd/rat for 2 years. There were 25 rats in each exposure group and 75 in the control group. When the experiment was terminated after 750 days, between 11 and 17 animals remained in each of the exposed groups and 32 of the controls. During the experimental period, four animals in the highest exposure group developed sarcomas at the injection site. One animal from each of the other exposure groups also developed sarcomas. Microscopic examination of prostates did not disclose any signs of neoplastic or preneoplastic changes in the prostate gland. Slight epithelial hyperplasia was seen to the same degree in controls and exposed animals. It should be noted that all animals in the two lowest exposure groups were not examined. A few tumors in other organs were observed, both in controls and exposed animals. There was no consistent pattern of appearance. Cadmium was analyzed in organs but accurate data could not be obtained since some tissues had dried during storage. However, the renal concentrations of cadmium must have been at least 100 mg/kg whole kidney in the highest exposure group.

Levy and Clark (*26*) and Levy et al. (*27*) gave rats and mice weekly doses by stomach tube for 2 years. In the rat experiment (*26*) there were three exposed groups with 30 rats in each and 90 controls. Cadmium was given as cadmium sulfate in doses of 0.087, 0.18, and 0.35 mg Cd/kg body weight. The mice were given 0.44, 0.88, and 1.75 mg Cd/kg body weight. The number of mice in each exposed group was 50 and in the control group 150. At the end of the experiment, between 8 and 17 rats remained in the exposed groups and 52 in the control rats, whereas corresponding figures for the mice were 42 to 47 and 125. In neither of the experiments did histological examination of the prostate gland reveal any neoplastic or preneoplastic changes, nor was there any increased incidence of tumors in other organs among exposed animals, compared to controls. Determination of cadmium in rat kidneys showed that concentrations varied between 2.8 and 10.1 mg/kg, comparable to values found in human nonsmokers with "normal" exposure to cadmium (*40*). Cadmium was not determined in tissues from mice, but it can be calculated that cadmium concentrations in mouse kidneys must have been very low as well. These low values are explained by the low absorption of cadmium in rats and mice (*1*).

Scott and Aughey (*61*) examined prostate glands of 50 rats given from 1 to 5 subcutaneous injections of 5.6 mg Cd as the chloride. The average weight of the animals was reported to be 70 g, which means that the given doses should correspond to 80 to 400 mg Cd/kg body weight, i.e., lethal doses. It is not reported how many of the 50 rats died, nor is length of observation time after injections given. However, the authors stated that "a possible early adenocarcinoma has been found."

When discussing the experimental induction of cancer of the prostate it must be remembered that the prostate gland in rodents is quite different from that of humans. Monkeys and dogs to some extent are comparable to humans in that respect, but there are no data on cadmium effects on the prostate of these animals. It must also be kept in mind that while cancer of the prostate is an extremely common disease in human beings of

advanced age, the incidence of this cancer is very low in laboratory animals. An extensive review on prostatic carcinoma in laboratory animals has recently been published (*62*). In recent years, adenocarcinomas of the prostate have been produced in rats and it has been suggested that these tumor types might be suitable as a model for human cancer of the prostate (*63*, *64*).

Epidemiological Studies on Cancer Morbidity and Mortality in Cadmium-Exposed People

The first reports of an increased number of deaths from cancer of the prostate among cadmium workers came from England, where the mortality among cadmium workers was examined by Potts (*65*). Results from Potts' limited study initiated a larger investigation by Kipling and Waterhouse in 1967 (*23*). Cases reported by Potts are included in the latter study described in the following.

The study comprised 248 men with a minimum exposure of one year to cadmium oxide dust. It is mentioned in this very brief report that the cause of death among the deceased was ascertained and that the expected number of cases of cancer was calculated by using a regional cancer registry. The authors stated that the total incidence of cancer did not differ between the groups and that there was a significant increase in the number of prostatic cancers, four observed cases against an expected number of 0.58. There was no indication of an increased risk for bronchial cancer.

Humperdinck reported in 1968 (*24*) that among 536 German workers employed any time during 1949 to 1966, and exposed to cadmium, there were five cases of cancer and no apparent relationship between cadmium exposure and cancer. However, 269 of the workers had been exposed for less than one year and only four had been exposed for more than seven years. There was no mention of any cancer of the prostate. Holden in 1969 (*25*) reported one case of cancer of the prostate among 42 workers exposed to cadmium oxide fumes for 2 to 40 years.

Lemen et al. (*29*) studied mortality in a cohort of workers occupationally exposed to cadmium oxide fumes or dust in a smelter. This smelter was mainly concerned with the refining of cadmium from preprocessed ore, which means that concentrations of other metals or metalloids were relatively low. In the 1940's, cadmium concentrations in air had been reported to be several milligrams per cubic meter, and concentrations measured in 1973 showed values up to 24 mg/m^3. Generally, however, concentrations were below 1 mg/m^3. In 1973, arsenic concentrations were around 1 μg/m^3. No data on arsenic levels in the 1940's are available. The cohort studied consisted of 292 white males, exposed for at least two years between 1940 and 1969. In 1974, 180 members of the cohort were alive and 92 had died. Data could not be obtained for the remaining 20 who were considered to be alive. Expected cause-specific number of deaths were calculated from statistics for the whole US white male population. In the cohort, 99 deaths were expected as compared to the 92 observed. In 27 cases the cause of death was cancer, whereas 17.5 were expected. There was a significant excess of cancer of the respiratory tract, SMR being 235, but no data on somking habits are given. There were four deaths from cancer of the prostate, as contrasted to 1.15 expected. It could not be proven statistically that this constituted an increased risk, but when the time interval from onset of exposure was taken into account it could be shown that there was an increased risk for cancer of the prostate. This calculation showed four observed, as contrasted to 0.88 expected, 20 years or more after onset of cadmium exposure. These four cases are presented in a table which shows that one man who died in 1972 was exposed between 1940 and 1944, when he was 39 to 43 years old. Nothing is reported about his occupation before 1940 or after 1944 until retirement. In the other three cases, the duration of exposure was between 13 and 18 years. In two of these cases exposure began already in the 1920's and ended in the 1940's. Thus, the main exposure was during times when no measurements of cadmium in air or other constituents were undertaken, but it may be presumed that they were exposed to high concentrations of airborne cadmium. Unfortunately, no data on arsenic concentrations in the 1920's are available. The authors concluded that the results "implicate cadmium exposure as the cause of certain types of malignant disease." Another major study is by Kjellström et al. (*33*). In the battery factory described by Friberg (*42*) all workers alive in 1959 were studied. They had more than five years of exposure and had been employed in 1945 or started working after that year. The changes in exposure since 1945, when cadmium concentrations in air were several mg Cd/m^3 have been reported (*37*, *43*) and the present exposure is generally less than 15 μg/m^3 (*38*). Many workers had already started work in the 1920's but no exposure data are available from this time. The workers had also been exposed to considerable amounts of nickel hydroxide dust. All workers diagnosed as having cancer during the years 1959-1975 were identified in the Swedish Cancer Registry. Of 269 male workers born between 1874 and 1952, 15

cases of cancer had been diagnosed. It was calculated from the national incidence rates that 16.4 new cases would have occurred. With regard to specific causes, no significant increase could be found except for cancer of the nasal pharynx. Two cases were found, whereas only 0.2 were expected. This was thought to be caused by nickel exposure. Two prostatic cancers were found, while 1.2 were expected. The corresponding figures for lung cancer were 2 and 1.35. Five cancers of the colon or rectum were found against 2.25 expected.

Kjellström et al. also investigated a cadmium-copper alloy plant, where the workers had been exposed to cadmium oxide fumes. In that factory cadmium in air was not determined until the middle of the 1960's, when concentrations were 100 to 400 μg Cd/m^3. Present exposure levels are lower. Workers who had been employed in 1940 or started work after that year and with at least five years of exposure, were studied. In this study the prostatic cancer deaths among 94 exposed men were compared to prostatic cancer deaths among 328 workers employed in the same factory but in another type of production. Expected numbers of death of cancer of the prostate were calculated from reports from the Swedish National Bureau of Statistics. Among the cadmium exposed workers, four cases were observed against 2.69 expected, and in the reference group, four were observed as compared to 6.42 expected. Thus, in these two studies there was also a tendency to an increase of prostatic cancers among cadmium exposed workers. However, it could not be statistically proven that there was a real difference.

There are two other studies (*30*, *31*) which have been extensively quoted in the literature as evidence for cadmium causing renal cancer and prostate cancer, respectively. There are, however, no data at all on cadmium exposure in these reports.

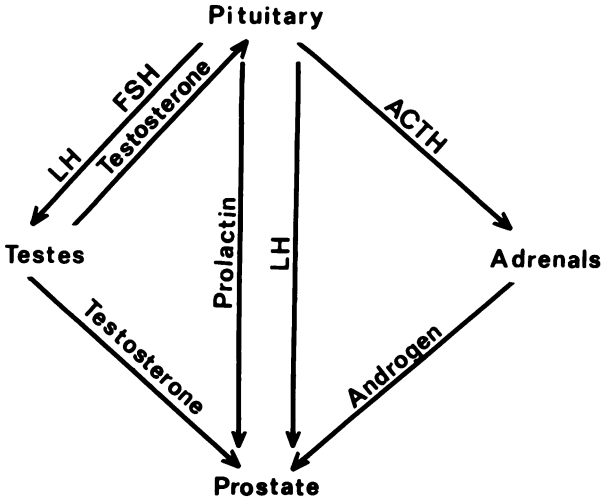

FIGURE 1. Major hormonal influences on the prostate.

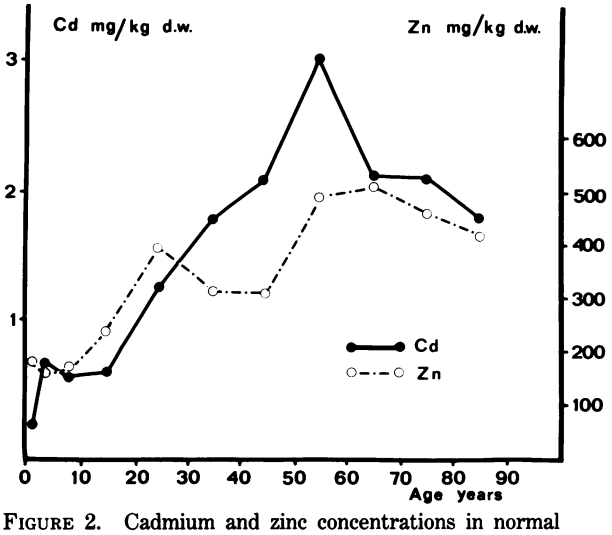

FIGURE 2. Cadmium and zinc concentrations in normal prostates (*73*).

The Prostate

Physiology, Biochemistry, and Metal Metabolism

The development and growth of the prostate, a genital accessory gland, is regulated by hormones. Figure 1 shows some of the more important endocrine glands and their influence on the prostate. An important factor is testosterone, which is produced in the testes. Testosterone production is in turn stimulated by pituitary hormones, especially LH. There may also be a direct pituitary influence through prolactin, which is thought to regulate the uptake of androgens in the prostate. Also the adrenal androgens may have an influence. Among the metals, zinc is outstanding. The highest concentrations are found in seminal plasma and the prostate (*66-74*). Zinc uptake has also been shown to be regulated by hormones (*75*, *76*). There are large differences in zinc concentrations within the prostate. Intraglandular variations are larger than interglandular (*70*). Zinc is mainly localized in the epithelial cells (*74*). It has been shown in rats that great cyclic variations in uptake of zinc may occur (*75-77*). Zinc is eliminated from the prostate via seminal fluid and is of importance for the viability motility, and fertility of human spermatozoa (*67*, *68*, *78*, *79*).

Zinc and cadmium concentrations in normal human tissue according to age are shown in Figure 2. The

data are from a study by Heinzsch et al. (*73*). A relationship between zinc and cadmium concentrations in prostatic tissue was reported by Habib (*80*). However, it has earlier been claimed by the same author that there were no correlations between cadmium and zinc in hypertrophic or carcinomatous tissues (*71*). Figures 3 and 4 show the relationship between prostatic cadmium and renal and liver cadmium [data taken from Hienzsch et al. (*73*) and Anke et al. (*81*)].

Data used for construction of Figures 2 to 4 are shown in Table 1, together with data from other studies where cadmium in the prostate and in the testicles has been determined. Heinzsch et al. (*73*) included their cases above 50 years of age among the "normals" though probably a very large proportion of these men have had prostatic hypertrophy.

It is not possible to draw any clear conclusions about the cadmium levels in different diseases of the prostate from the available data. The few data available on testicular cadmium in normal people indicate that the level in this organ will be of the same magnitude as in the prostate. Regarding excessive exposure to cadmium there is one case with heavy environmental exposure to cadmium (*84*) and three occupationally exposed men (*59*). Prostatic cadmium as well as testicular cadmium had reached high concentrations and again there is an indication that testicular concentrations will be of the same magnitude as prostatic concentrations.

Also animal data indicate that there is a parallel accumulation in the prostate and in the testicles. Nordberg (*55*) found in mice given 0.25 mg Cd/kg subcutaneously 5 days a week during 6 months that the average concentration of cadmium in the prostate was 5.44 and in the testicles 4.45 mg/kg wet weight. In mice given the double dose, the concentrations were 11.45 and 8.23 mg/kg, respectively.

Epidemiology of Cancer of the Prostate

Cancer of the prostate is one of the most common causes of death from cancer, especially in some European countries and in the USA. It has thus attracted great interest and initiated a large number of reviews and epidemioliogical studies (*85-107*). As for other forms of cancer, there have been changes in the diagnosis and classification of the disease, and changes in incidence sometimes have been difficult to evaluate. The disease is very rare in men under age 50, and it is strongly influenced by hormonal status since it does not develop in men castrated before age 40. There are large differences between countries with regard to the occurrence of the disease. Thus the non-white population in the U.S. and Sweden have among the highest death rates of cancer of the prostate, whereas Japan has among the lowest (*85*). Cancer of the prostate without clinical manifestations, latent prostatic carcinoma, is as common in Japanese living in Japan as in Japanese living in the U.S. (Hawaii) (*86*), whereas the mortality from cancer of the prostate among Japanese in the U.S. (Hawaii) is higher than in Japan. This is an important fact to remember, since exposure to cadmium in Japan is considerably higher than in both the USA and Sweden. This indicates that "normal" exposure to cadmium is of little importance for the development of the clinical manifestations of cancer of the prostate. However, as will be discussed later, this does not exclude the possibility that extreme exposure to cadmium might have an influence.

The occurrence of latent carcinoma in seven areas around the world was studied by Breslow et

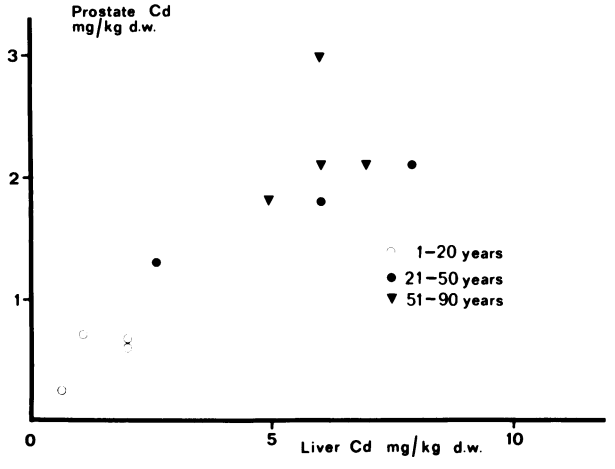

FIGURE 3. Cadmium in prostate in relation to liver cadmium (*73,81*).

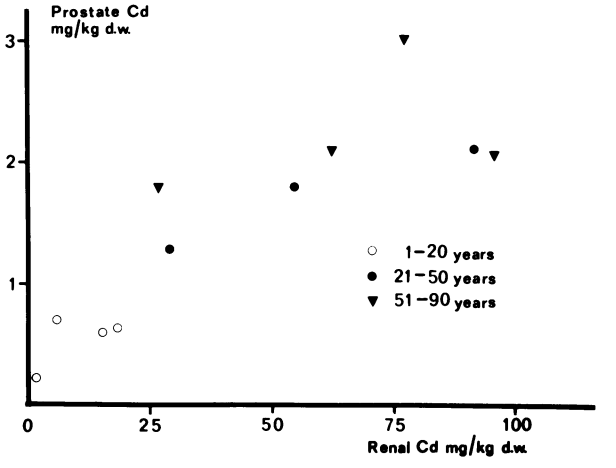

FIGURE 4. Cadmium in prostate in relation to renal cadmium (*73, 81*).

Table 1. Cadmium and zinc in prostate and cadmium in kidney, liver and testicles from normal men (N), men with benign prostatic hyperthrophy (BPH), cancer of the prostate (CaP), men exposed to cadmium in the general environment (E) and occupationally exposed men (O).

		Metal concn (mg/kg dry weight)						
			Prostate		Kidney	Liver	Testicles	Ref.
	Age	*n*	Cd	Zn	Cd	Cd	Cd	
N	1	10	0.26	183	1.3	0.67		(*73*)
	2–5	10	0.72	160	5.4	1.1		(*73*)
	6–10	10	0.61	167	15	2.0		(*73*)
	11–20	10	0.65	238	18	2.0		(*73*)
	21–30	10	1.3	396	29	2.6		(*73*)
	31–40	10	1.8	311	55	6.0		(*73*)
	41–50	10	2.1	310	92	7.9		(*73*)
	51–60	10	3.0	485	78	5.9		(*73*)
	61–70	10	2.1	520	96	6.9		(*73*)
	71–80	10	2.1	456	62	6.0		(*73*)
	81–90	10	1.8	419	27	4.9		(*73*)
	40–70	17			70	10	2.3	(*81*)
	40–80	20			133	13	4.1	(*81*)
	36	9	0.58	445				(*71*)
	10–60	15			180	11	2.6	(*83*)
	49	1	0.90		40	7	0.95	(*59*)
	56	1	0.85		47	7	0.8	(*59*)
	56	1	0.50		60	10	1.0	(*59*)
BPH	41–90	?	1.1					(*73*)
	70	23	2.58	449				(*71*)
	?	15	0.61[a]	555				(*80*)
CaP	41–90	?	0.62					(*73*)
	73	9	14.5	170				(*71*)
E	83	1			270	317	70	(*84*)
O	46	1	185		500	550	170	(*59*)
	55	1	90		1200	1035	45	(*59*)
	67	1			550	224	3.5	(*59*)

[a] Calculated from Habib (*80*).

al. (*87*). Consecutive autopsies were made of persons without clinical signs of prostatic cancer. Standardized methods were used to obtain specimens from the same parts of the prostate. Microscopic examination was made by the original pathologist and on a blind basis by other participating pathologists. Carcinomas were classified as small, medium or large. Small carcinomas occurred in about 12 percent of all cases and did not vary with area or with age. Medium and large latent carcinomas were common in Sweden, West German, and Jamaica (26.8, 18.5, and 17.9%) whereas a low frequency was found in Hong Kong, Israel, and Singapore (6.9, 5.6, and 5.0%). In Uganda the frequency was 10%. There was increase with age, occurring on an average of 4.6% in the age group 45-54 and 28.7% in the age group 75 years and over. The frequencies correspond to the mortality from prostatic cancer in the studied areas. This study indicates that the inducing factor occurs to the same extent in many areas, but that promoting factors may vary to a large extent.

In a recent study by Hölund (*88*) latent cancer of the prostate was found on in about 22% of a series of consecutive autopsies in Denmark. The frequency was 10% in age group 50-59 and 26% in age group 70-79.

In addition to the earlier mentioned studies on prostatic cancer among cadmium exposed workers, there are many studies where other factors thought to be of importance for cancer of the prostate have been investigated. Among such factors are occupation, race, sex life, socioeconomic status, and nutrition.

In 1931, the relationship between cancer of the prostate and certain occupations was studied (*89*). Henry et al. studied cancer of the bladder and cancer of the prostate, and whereas they could find that cancer of the bladder was related to certain occupations, no consistent pattern appeared with regard to cancer of the prostate. A study of more historical interest was published in 1949 by Versluys (*90*) who reported data on cancer in the Netherlands during the years 1931-1935. In that study it was found that people with university education, especially clergymen, had an increased incidence of

cancer of the prostate. In later years there have been several studies on rubber workers (*31, 91-93*) but no consistent pattern has appeared with regard to cancer of the prostate and when an excess of prostatic cancers was found, exposure to cadmium could not be demonstrated (*93, 94*). Metal workers were examined by Houten et al. (*95*). Blacksmiths, mechanics, and repairmen showed, according to the authors, significantly elevated risks for cancer of the prostate. In the group "furnace-men, smeltermen and pourers" there did not seem to be an increased risk for cancer of the prostate. In several other occupations where exposure to metals might have occurred, such as mine workers, the relative risk seemed to be increased but not significant.

A recent study designed especially to study the relationship between prostatic cancer and occupation was reported by Ernster et al. (*94*). They studied deaths of prostatic cancer in two California counties using the case-control method. In the two counties, 368 and 334 prostatic cancer deaths were found. Matching was done for age and race. The authors concentrated on occupations where elevated numbers were seen in both counties. A broad occupational spectrum was found. Bookkeepers, shipping and receiving clerks, compositors and type-setters and ship-fitters were found to have an increased risk. Persons working in fields such as horticultural services, newspaper publishing and printing, motor vehicle sales, drug-stores, drugs, chemicals and allied products, as well as miscellaneous personal services showed elevated incidence of cancer of the prostate. These results indicate, as well as earlier mentioned studies, that there is no consistent pattern for cancer of the prostate with regard to occupation.

Another major study is by Williams et al. (*96*) who used data from the Third National Cancer Survey Interview in the USA. They studied cancer patients who had been interviewed and about whom extensive information on occupation could be obtained. In that study, it was found that prostate cancer was more common among ministers, farmers, plumbers, rubber workers, coal miners and two types of retailers. This once again indicates the broad spectrum of occupations where an excess might be found. The following is a quote from the report: "A positive association between prostate cancer and men working for non-profit organizations was localized entirely to older men who were well educated nonsmokers and nondrinkers (probably the clergymen found associated in the analysis of occupation)." It was earlier mentioned that results from a study in the Netherlands (*87*) indicated that clergymen had an increased risk for developing cancer of the prostate. In this context it is also of interest to mention that among active Mormons (men who live according to the "Word of Wisdom") the mortality from most types of cancer forms unrelated to smoking is much lower than for nonsmoking white males in the U.S. One exception is cancer of the prostate, which was the most common cancer among active Mormon males in Utah (*97*). In fact, intake of alcohol might have a protective effect, since the incidence of prostatic cancer is lower among patients with liver cirrhosis. A decreased breakdown of estrogen is thought to be the reason for this finding (*85*). Alcohol may also have a direct effect on the production of testosterone in the testes (*98-100*). The metabolite, acetaldehyde, can also have an influence (*99*).

Cancer mortality among printers has been studied by Green et al. (*101*) who found an excess only among non-white printers. This was a proportionate mortality study, and it is difficult to compare with earlier mentioned studies. In some of the earlier papers (*87, 94*) printers seemed to have an increased risk for cancer of the prostate. It was stated that there was no association between prostatic cancer and cadmium exposure, but it is not clear whether cadmium concentrations in air were determined. In two studies on ferrochromium workers in Norway and Sweden (*102, 103*) a slight increase was found in the incidence of prostatic cancer. Espeically maintenance workers showed an excess.

The relationship between marital status and cancer of the prostate has been investigated in several studies. Thus, Versluys (*90*) concluded that cancer of the prostate was found more frequently in married people and those who had been married. Lancaster (*104*) found in Australia that cancer of the prostate was more common among married men with children than among married men without children or men who had never married. King et al. (*105*) in an extensive review on the epidemiology of cancer of the prostate concluded: "Persons who had ever married have a higher frequency of cancer of male genital organs than those who remained single." According to King et al., cancer of the prostate is the form of cancer which in both white and nonwhite shows the highest ratio of ever-married males to single males. Among the ever married men it was also indicated that there was a higher mortality among the widowed and divorced men.

Greenwald et al. (*106*) studied the relationship between widowerhood and cancer of the prostate and concluded that earlier data, showing higher rates of prostate cancer among widowers, might be influenced by artefacts of classifying in vital records. Furthermore, Greenwald et al. (*107*) did not

find that martial status was a factor of importance in the development of cancer of the prostate. Even though a statistical significance was not obtained in that study, there was an indication among the prostate cancer patients of a lower number without children than among controls.

In addition to marital status attempts have also been made to relate sexual activity and habits to cancer of the prostate (*108, 109*). In one of these studies (*108*) it was claimed that delayed sexual development might be one factor of importance for the development of prostatic cancer and that early repression of sexuality and premature cessation of sexuality also could contribute. However, in this study it was also reported that occupational exposure to fertilizers and auto exhaust fumes were more common among prostatic cancer patients than among controls.

Marital status and cancer was also studied by Ernster et al. (*110*) using data from the Third National Cancer Survey. With regard to prostatic cancer they found that single men had lower incidence rates than married men who in turn had lower rates than widowers. It was also found that married persons generally had low rates for death from all causes combined.

That race might be a factor has already been mentioned. In the U.S. the mortality rate for nonwhites has increased markedly during the last decades and is now considerably higher than among the whites (*111-115*). This difference is thought not to depend on socioeconomic factors (*111*). Black populations in Africa and the West Indies have lower prostatic cancer mortality rates than U.S. blacks (*85, 112*). Death from cancer of the prostate is uncommon in Japan, but it should be kept in mind that in Japan there has been an increase in prostatic cancer mortality from about 0.5/100,000 to about 2/100,000 from 1950 to 1963, a 4-fold increase. During the same period, the rate increased from about 17/100,000 among U.S. nonwhites to 22/100,000 and showed a slight decrease from about 13/100,000 to 11/100,000 among U.S. whites. In Sweden, the corresponding figures were about 12 and 18/100,000 (*86*). In a recent study (*113*) it was shown that among Japanese living in two counties in California, prostatic cancer constituted about 14 and 3.5% of total cancer deaths, respectively, whereas the corresponding figure in Japan is less than 1%. In the same study it was also found that Chinese in California had lower incidence of prostatic cancer than U.S. whites, the figures being similar to the Japanese in USA.

In the U.S., cancer of the prostate is more common in counties where Scandinavian descendants reside (*115*). The higher incidence among U.S. blacks has also been related to population density (*105, 115*). Otherwise, regional differences in the U.S. are relative small. Among the whites there was only an 8% difference between regions with the lowest and the highest mortality rates (*115*).

Religion has also been implied as a factor (*85, 105*), Protestants in the U.S. having a higher death rate than Catholics and Jews (*105*). Dietary factors, especially intake of fat, must also be taken into account (*16*). Hill et al. (*117*) gave black South African men, who ordinarly had a vegetarian diet, a Western diet high in fat and animal protein for 3 weeks. Black and white North American men, ordinarily on a Western diet, were given a vegetarian diet for 3 weeks. Urinary excretion of androgens and estrogens before the experimental diet was found to be much lower in the South African men than in black or white Americans. The experimental diets caused an increase in the excretion of androgens and estrogens of the black South Africans and a decrease among the black and white North Americans. These data give strong support that diet is a main factor and that the racial differences in mortality from prostatic cancer to a large extent depend on the dietary habits. It is, however, not clear if this can fully explain the difference between the whites and the blacks in the U.S.

There are still other factors which could be discussed, but the above mentioned data may indicate the extreme complexicity of the etiology of cancer of the prostate and how incomplete present knowledge is. Even the Kinsey report has been quoted (*105*) as giving clues to the etiology.

Can Cadmium Induce Cancer of the Prostate?

The fact that the frequency of small latent cancers is about the same in countries with large differences in deaths from prostatic cancer indicates that males all over the world probably have the same chance of developing this type of cancer. Exogenous and endogenous factors, e.g. nutrition, sex life, and liver function, will then decide to what extent the cancer becomes clinically manifest.

If low level exposure to cadmium is a factor for inducing the cancer, it could be expected that the latent cancer would be more common among Japanese in Japan, whereas Japanese in the US would have less. In fact the prevalence is the same. This does not mean that excessive occupational exposure may not induce prostatic cancer, rather that it may not be right to extrapolate from data obtained in occupational studies to "normal" exposure levels.

Theoretically, cadmium can influence the prostate in several ways. As previously mentioned, high cadmium concentrations have been found in prostates of men exposed to excessive amounts of cadmium. A direct interaction with zinc is thus possible. It has been demonstrated that in carcinomatous prostatic tissues there are increased levels of testosterone and androstenodione whereas dehydrotestosterone levels are decreased (*118*, *119*). In a brief report (*120*) it was stated that a zinc-binding protein, similar to metallothionein, was found in normal and hypertrophic prostatic tissue. This protein was claimed to have some affinity for androgens. The authors speculated that a slight shift in the hormone/metal balance may induce cancer of the prostate. Wallace and Grant (*121*) have postulated that when epithelial cells in the prostate are saturated with zinc, this will stop the reduction of testosterone to dehydrotestosterone by thiol groups. When zinc is lost via seminal fluid, the activity of 5-α-reductase is restored. Dehydrotestosterone is again produced and this will in turn stimulate new incorporation of zinc in the cells. Theoretically, accumulation of cadmium could cause permanent binding of thiol groups and thus cause an accumulation of testosterone which could induce or promote cancer. Accumulation of cadmium in the testes, on the other hand, might decrease testosterone levels, which theoretically would have a protective effect. Another possibility is that accumulation of cadmium in the pituitary gland could cause changes in prolactin and LH production.

The accumulation of cadmium in liver and kidney causes an accumulation of zinc in these organs and it has been shown in animal experiments that if the zinc intake is marginal, cadmium exposure will cause a decrease in testicular concentration of zinc (*122*) as well as decreased testosterone production (*58*). There are no data on prostatic concentrations of zinc in cadmium exposed animals or humans. However, the intake of zinc is marginal for many humans and it is conceivable that in heavily exposed cadmium workers a relative zinc deficiency may exist which together with accumulation of cadmium might contribute to the theoretical mechanisms explained above.

All reported cases of excess deaths from prostatic cancer among cadmium exposed workers refer to workers with heavy exposure. It is conceivable that both high prostatic cadmium concentration and a disturbed zinc metabolism may have existed in these workers. In these studies no attention has been paid to the other factors mentioned in the context of the general epidemiology of prostatic cancer. Martial status, fertility, sexual habits, nutrition etc. should be taken into account in further studies on occupationally exposed workers.

Even if there is a higher incidence of deaths from prostatic cancer among heavily exposed workers it does not seem reasonable to extrapolate to low level exposure. If there is a cancer-promoting action from large doses of cadmium, it is probably indirect, mediated through the hormonal systems regulating metabolism of prostatic cells.

REFERENCES

1. Friberg, L., Piscator, M., Nordberg, G. F., and Kjellström, T. Cadmium in the Environment. CRC Press, Cleveland, 2nd ed., 1974.
2. NIOSH. Criteria for a Recommended Standard—Occupational Exposure to Cadmium. HEW No 76-192. National Institute for Occupational Safety and Health, US Department of Health, Education and Welfare, Rockville, MD., 1976.
3. Umweltbundesamt. Luftqualitätskriterium für Cadmium. Berichte 4/77. Umweltbundesamt, Berlin, 1977.
4. CEC. Evaluation of the Impact of Cadmium on the Health of Man. Commission of the European Communities, Luxembourg, 1977.
5. Tsuchiya, K., Ed. Cadmium Studies in Japan—a Review. Kodanska Ltd., Tokyo, and Elsevier/North Holland Biomedical Press, Amsterdam, 1978.
6. WHO. Environmental Health Criteria for Cadmium. Interim Report. World Health Organization, Geneva, 1979.
7. EPA. Health Assessment Document for Cadmium. EPA-600/8-79-003. U.S. Environmental Protection Agency, Research Triangle Park, N.C., 1979.
8. Friberg, L., Kjellström, T., Nordberg, G. F., and Piscator, M. Cadmium. In: Handbook on the Toxicology of Metals. L. Friberg, G. F. Nordberg and V. B. Vouk, Eds., Elsevier/North-Holland Biomedical Press, Amsterdam, 1979, pp. 355-381.
9. WHO. Health-Based Permissible Levels for Occupational Exposure to Cadmium. World Health Organization, Geneva, 1980.
10. Webb, M., Ed. The Chemistry, Biochemistry and Biology of Cadmium. Elsevier/North-Holland Biomedical Press, Amsterdam, 1979.
11. Haddow, A., Dukes C. E., and Mitchley, B. C. V. Carcinogenicity of iron preparations and metal-carbohydrate complexes. Rep. Brit. Emp. Cancer Campgn. 39: 74 (1964).
12. Haddow, A., Roe, F. J. C., Dukes, C. E., and Mitchley, B. C. V. Cadmium neoplasia: sarcomata at the site of injection of cadmium sulphate in rats and mice. Brit. J. Cancer 18: 667 (1964).
13. Roe, F. J. C., Dukes, C. E., Cameron, K. M., Pugh, R. C. B., and Mitchley, B. C. V. Cadmium neoplasia: testicular atrophy and leydig cell hyperplasia and neoplasia in rats and mice following the subcutaneous injection of cadmium salts. Brit. J. Cancer 18: 674 (1964).
14. Gunn, S. A., Gould, T. C., and Anderson, W. A. D. Cadmium-induced interstitial cell tumors in rats and mice and their prevention by zinc. J. Nat. Cancer Inst. 31: 745 (1963).
15. Gunn, S. A., Gould, T. C., and Anderson, W. A. D. Effect of zinc on cancerogenesis by cadmium. Proc. Soc. Exptl. Biol. Med. 115: 653 (1964).
16. Heath, J. C., Daniel, M. R., Dingle, J. T., and Webb, M. Cadmium as a carcinogen. Nature 193: 592 (1962).
17. Kazantzis, G., and Hanbury, W. J. The induction of sarcoma in the rat by cadmium sulphide and cadmium oxide. Brit. J. Cancer 21: 190 (1966).

18. Gunn, S. A., Gould, T. C., and Anderson, W. A. D. Specific response of mesenchymal tissue to cancerogenesis by cadmium. Arch. Pathol. 83: 493 (1967).
19. Kanisawa, M., and Schroeder, H. A. Life term studies on the effect of trace elements on spontaneous tumors in mice and rats. Cancer Res. 29: 892 (1969).
20. Schroeder, H. A.. Balassa, J. J., and Vinton, W. H., Jr. Chromium, lead, cadmium, nickel and titanium in mice: effect on mortality, tumors and tissue levels. J. Nutr. 83: 239 (1964).
21. Schroeder, H. A., Balassa, J. J., and Vinton, W. H., Jr. Chromium, cadmium and lead in rats: effects on life span, tumors and tissue levels. J. Nutr. 86: 51 (1965).
22. Levy, L. S., Roe, F. J. C., Malcolm, D., Kazantzis, G., Clack, J., and Platt, H. S. Absence of prostatic changes in rats exposed to cadmium. Ann. Occup. Hyg. 16: 111 (1973).
23. Kipling, M. D., and Waterhouse, J. A. H. Cadmium and prostatic carcinoma (letter). Lancet 1: 730 (1967).
24. Humperdinck, K. Kadmium und Lungenkrebs. Med. Klin. 63: 948 (1968).
25. Holden, H. Cadmium toxicology (letter). Lancet 2: 57 (1969).
26. Levy, L. S., and Clack, J. Further studies on the effect of cadmium on the prostate gland—I. Absence of prostatic changes in rats given oral cadmium sulphate for two years. Ann. Occup. Hyg. 17: 205 (1975).
27. Levy, L. S., Clack, J., and Roe, F. J. C. Further studies on the effect of cadmium on the prostate gland—II. Absence of prostatic changes in mice given oral cadmium sulphate for eighteen months. Ann. Occup. Hyg. 17: 213 (1975).
28. Löser, E. A 2 year oral carcinogenicity study with cadmium on rats. Cancer Lett. 9: 191 (1980).
29. Lemen, R. A., Lee, J. S., Wagoner, J. K., and Blejer, H. P. Cancer mortality among cadmium production workers. Ann. N.Y. Acad. Sci. 271: 273 (1976).
30. Kolonel, L. N. Association of cadmium with renal cancer. Cancer 37: 1782 (1976).
31. McMichael, A. J., Spirtas, R., Gamble, J. F., and Tousey, P. M. Mortality among rubber workers: relationship to specific jobs. J. Occup. Med. 18: 178 (1976).
32. IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Man. Cadmium, Nickel, some Epoxides, Miscellaneous Industrial Chemicals and General Considerations on Volatile Anaesthetics. Vol. 11. International Agency for Research on Cancer, Lyon, 1976.
33. Kjellström, T., Friberg, L., and Rahnster, B. Mortality and cancer morbidity among cadmium-exposed workers. Environ. Health Perspect. 28: 199 (1979).
34. Kjellström, T. Exposure and accumulation of cadmium in populations from Japan, the United States, and Sweden. Environ. Health Perspect. 28: 169 (1979).
35. Piscator, M. Exposure to cadmium. In: Trace Metals. Exposure and Health Effects. E. Di Ferrante, Ed., Pergamon Press, Oxford and New York, 1979.
36. Flanagan, P. R., McLellan, J. S., Haist, J., Cherian, M. G., Chamberlain, M. J., and Valberg, L. S. Increased dietary cadmium absorption in mice and human subjects with iron deficiency. Gastroenterology 74: 841 (1978).
37. Adamsson, E. Long-term sampling of airborne cadmium dust in an alkaline battery factory. Scand. J. Work Environ. Health 5: 178 (1979).
38. Adamsson, E., Piscator, M., and Nogawa, K. Pulmonary and gastrointestinal exposure to cadmium oxide dust in a battery factory. Environ. Health Perspect. 28: 219 (1979).
39. Elinder, C.-G., Kjellström, T., Friberg, L., Lind, B., and Linnman, L. Cadmium in kidney cortex, liver, and pancreas from Swedish autopsies. Arch. Environ. Health 31: 292 (1976).
40. Kägi, J. H. R., and Nordberg, M., Eds. Metallothionein. Proceedings of the First International Meeting on Metallothionein and other Low Molecular Weight Metal-binding Proteins, Zürich, July 17-22, 1978, Birkhäuser, Basel-Boston-Stuttgart, 1979.
41. Nordberg, M., and Kojima, Y. Metallothionein and other low molecular weight metal-binding proteins. In: Metallothionein. J. H. R. Kägi and M. Nordberg, Eds. Birkhäuser, Basel-Boston-Stuttgart, 1979.
42. Friberg, L. Health Hazards in the Manufacture of Alkaline Accumulators with Special Reference to Chronic Cadmium Poisoning. Acta Med. Scand. 138 (suppl.): 240 (1950).
43. Kjellström, T., Evrin, P.-E., and Rahnster, B. Dose-response analysis of cadmium-induced tubular proteinuria, a study of urinary β_2-microglobulin excretion among workers in a battery factory. Environ. Res. 13: 303 (1977).
44. Kazantzis, G., Flynn, F. V., Spowage, J. S., and Trott, D. G. Renal tubular malfunction and pulmonary emphysema in cadmium pigment workers. Quart. J. Med. 32: 165 (1963).
45. Lauwerys, R. R., Buchet, J. P., Roels, H. A., Brouwers, J., and Stanescu, D. Epidemiological survey of workers exposed to cadmium. Effect on lung, kidney, and several biological indices. Arch. Environ. Health 28: 145 (1974).
46. Kjellström, T., Shiroishi, K., and Evrin, P.-E. Urinary β_2-microglobulin excretion among people exposed to cadmium in the general environment. Environ. Res. 13: 318 (1977).
47. Piscator, M. Proteinuria in chronic cadmium poisoning. III. Electrophoretic and immunoelectrophoretic studies on urinary proteins from cadmium workers, with special reference to the excretion of low molecular weight proteins. Arch. Environ. Health 12: 335 (1966).
48. Piscator, M. Proteinuria in chronic cadmium poisoning. IV. Gel filtration and ion exchange chromatography of urinary proteins from cadmium workers. Arch. Environ. Health 12: 345 (1966).
49. Kjellström, T., and Piscator, M. β_2-microglobulin in cadmium nephrotoxicity. Phadedoc No 1, Pharmacia Diagnostics, Uppsala, Sweden, 1979.
50. Piscator, M., and Pettersson, B. Chronic cadmium poisoning—diagnosis and prevention. In: Clinical Chemistry and Chemical Toxicology of Metals. S. S. Brown, Ed., Elsevier/North-Holland Biomedical Press, Amsterdam, 1977.
51. Berlin, M., and Ullberg, S. The fate of ^{109} Cd in the mouse. An autoradiographic study after a single intravenous injection of $^{109}CdCl_2$. Arch. Environ. Health 7: 686 (1963).
51. Zielinska-Psuja, B., Lukaszyk, A., and Senczuk, W. The anti-reproductive effects of long term oral administration of cadmium on the adult male rat. Int. J. Andrology 2: 150 (1979).
53. Friberg, L., Kjellström, T., Nordberg, G. F., and Piscator, M. Cadmium in the Environment—III. A Toxicological and Epidemiological Appraisal. EPA-650/2-75-049. U.S. Environmental Protection Agency, Washington, D.C., 1975.
54. Piscator, M., and Axelsson, B. Serum proteins and kidney function after exposure to cadmium. Arch. Environ. Health 21: 604 (1970).
55. Nordberg, G. F. Effects of acute and chronic cadmium exposure on the testicles of mice. With special reference to protective effects of metallothionein. Environ. Physiol. Biochem. 1: 171 (1971).
56. Nordberg, G. F., and Piscator, M. Influence of long-term cadmium exposure on urinary excretion of protein and cadmium in mice. Environ. Physiol. Biochem. 2: 37 (1972).
57. Nordberg, G. F. Effects of long-term cadmium exposure on

the seminal vesicles of mice. J. Reprod. Fert. 45: 165 (1975).
58. Sanwal, M. C., Sing, R. D., Alverson, G., Srivastava, L. S., and Sholiton, L. J. Decreased testosterone synthesis in zinc deficient and cadmium exposed rats. Fed. Proc. 37: 890 (1978).
59. Smith, J. P., Smith, J. C., and McCall, A. J. Chronic poisoning from cadmium fume. J. Pathol. Bacteriol. 80: 287 (1960).
60. Favino, A., Candura, F., Chiappino, G., and Cavalleri, A. Study on the androgen function of men exposed to cadmium. Med. Lav. 59: 105 (1968).
61. Scott, R., and Aughey, E. Methylcholanthrene and cadmium induced changes in rat prostate. Brit. J. Urol. 50: 25 (1978).
62. Rivenson, A., and Silverman, J. The prostatic carcinoma in laboratory animals. A bibliographic survey from 1900 to 1977. Invest. Urol. 16: 468 (1979).
63. Müntzing, J., Kirdani, R. Y., Murphy, G. P., and Sandborg, A. A. A rat prostatic adenocarcinoma as a model for the human disease. Invest. Urol. 17: 37 (1979).
64. Drago, J. R., Ikeda, R. M., Maurer, R. E., Goldman, L. B., and Tesluk, H. The Nb rat: Prostatic adenocarcinoma model. Invest. Urol. 16: 353 (1979).
65. Potts, C. L. Cadmium proteinuria—the health of battery workers exposed to cadmium oxide dust. Ann. Occup. Hyg. 8: 55 (1965).
66. Schoenfeld, C., Amelar, R. D., Dubin, L., and Numeroff, M. Prolactin, fructose and zinc levels found in human seminal plasma. Fertil. Steril. 32: 206 (1979).
67. Skandhan, K. P., Skandhan, S., and Mehta, Y. B. Semen electrolytes in normal and infertile subjects. II. Zinc. Experientia 34: 1476 (1978).
68. Homonnai, Z. T., Matzkin, H., Fainman, N., Paz, G., and Kraicer, P. F. The cation composition of the seminal plasma and prostatic fluid and its correlation to semen quality. Fertil. Steril. 29: 539 (1978).
69. Gonick, P., Oberleas, D., Knechtges, T., and Prasad, A. S. Atomic absorption spectrophotometric determination of zinc in the prostate. Invest. Urol. 6: 345 (1969).
70. Kerr, W. K., Keresteci, A. G., and Mayoh, H. The distribution of zinc within the human prostate. Cancer 13: 550 (1960).
71. Habib, F. K., Hammond, G. L., Lee, I. R., Dawson, J. B., Mason, M. K., Smith, P. H., and Stitch, S. R. Metal-androgen interrelationships in carcinoma and hyperplasia of the human prostate. J. Endocrinol. 71: 133 (1976).
72. Habib, F. K., Mason, M. K., Smith, P. H., and Stitch, S. R. Cancer of the prostate: Early Diagnosis by zinc and hormone analysis?. Brit. J. Cancer 39: 700 (1979).
73. Hienzsch, E., Schneider, H. J., Anke, M., Hennig, A., and Groppel, B. The cadmium-, zinc-, copper-, and manganese-level of different organs of human beings without considerable Cd-exposure in dependence on age and sex. In: Kamium-Symposium. M. Anke and H. J. Schneider, Eds., Friedrich-Schiller-Universität, Jena, 1979.
74. Györkey, F., Min, K.-W., Huff, Y. A., and Györkey, P. Zinc and mangesium in human prostate gland: Normal, hyperplastic and neoplastic. Cancer Res. 27: 1348 (1967).
75. Gunn, S. A., Gould, T. C., and Anderson, W. A. D. Hormonal control of zinc in mature rat testis. J. Endorcinol. 23: 37 (1961).
76. Rosoff, B., and Martin, C. R. Effect of gonadotrophins and of testosterone on organ weights and zinc-65 uptake in the male rat. Gen. Comp. Endocrinol. 10: 75 (1968).
77. Gunn, S. A., and Gould, T. C. The presence of an inherent reproductive cycle in the male laboratory rat. J. Endocrinol. 17: 344 (1958).
78. Eliasoon, R. Semen analysis. Environ. Health Perspect. 24: 81 (1978).
79. Lindholmer, C. The importance of seminal plasma for human sperm motility. Biol. Reprod. 10: 533 (1974).
80. Habib, F. K. Zinc and the steroid endocrinology of the human prostate. J. Steroid Biochem. 9: 403 (1978).
81. Anke, M., Klinger, G., Grün, M., and Schneider, H.-J. The dependence of the Cd-concentration in animals and human beings on sex and age. In: Kadmium-Symposium, Jena, August 1-3, 1977. M. Anke and H.-J. Schneider, Eds. Friedrich-Schiller-Universität, Jena, 1979.
82. Schneider, H.-J., Anke, M., Grün, M., and Partschefeld, M. The Cd-, Zn-, Cu-, and Mn- level of different organs of human beings from an area exposed to Cd in comparison with standard values. In: Kadmium-Symposium, Jena, August 1-3, 1977. M. Anke and H.-J. Schneider, Eds. Friedrich-Schiller-Universität, Jena, 1979.
83. Sumino, K., Hayakawa, K., Shibata, T., and Kitamura, S. Heavy metals in normal Japanese tissues. Amounts of 15 heavy metals in 30 subjects. Arch. Environ. Health 30: 487 (1975).
84. Kyogoku, M. An autopsy report on Mr. Y. K. Kankyo Hoken Report, 36 (Supplement): 30 (1975).
85. Wynder, E. L., Mabuchi, K., and Whitmore, W. F. Epidemiology of cancer of the prostate. Cancer 28: 344 (1971).
86. Akazaki, K., and Stemmermann, G. N. Comparative study of latent carcinoma of the prostate among Japanese in Japan and Hawaii. J. Nat. Cancer Inst. 50: 1137 (1973).
87. Breslow, N., Chan, C. W., Dhom, G., Drury, R. A. B., Franks, L. M., Gellei, B., Lee, Y. S., Lundberg, S., Sparke, B., Sternby, N. H., and Tulinius, H. Latent carcinoma of prostate at autopsy in seven areas: Int. J. Cancer 20: 680 (1977).
88. Hölund, B. Latent prostatic cancer in a consecutive autopsy series. Scand. J. Urol. Nephrol. 14: 29 (1980).
89. Henry, S. A., Kennaway, N. M., and Kennaway, E. L. The incidence of cancer of the bladder and prostate in certain occupations. J. Hyg. 31: 125 (1931).
90. Versluys, J. J. Cancer and occupation in the Netherlands. Brit. J. Cancer 3: 161 (1949).
91. Andjelkovic, D., Taulbee, J., and Symons, M. Mortality experience of a cohort or rubber workers 1964-1973. J. Occup. Med. 18: 387 (1976).
92. Andjelkovic, D., Taulbee, J., Symons, M., and Williams, T. Mortality of rubber workers with reference to work experience. J. Occup. Med. 19: 397 (1977).
93. Monson, R. R., and Fine, L. J. Cancer mortality and morbidity among rubber workers. J. Natl. Cancer Inst. 61: 1047 (1978).
94. Ernster, V. L., Selvin, S., Brown, S. M., Sacks, S. T., Winkelstein, W., and Austin, D. F. A review and retrospective analysis based on death certificates in two California counties. J. Occup. Med. 21: 175 (1979).
95. Houten, L., Bross, I. D. J., Viadana, E., and Sonnesso, G. Occupational cancer in men exposed to metals. Adv. Exptl. Med. Biol. 91: 93 (1977).
96. Williams, R. R., Stegens, N. L., and Goldsmith, J. R. Association of cancer site and type with occupation and industry from the Third National Cancer Survey Interview. J. Natl. Cancer Inst. 59: 1147 (1977).
97. Enstrom, J. E. Cancer and total mortality among active mormons. Cancer 42: 1943 (1978).
98. Gordon, G. G., Altman, K., Southren, A. L., Rubin, E., and Lieber, C. S. Effect of alcohol (ethanol) administration on sex-hormone metabolism in normal men. New Engl. J. Med. 295: 793 (1976).

99. Cicero, T. J., Bell, R. D., Meyer, E. R., and Badger, T. M. Ethanol and acetaldehyde directly inhibit testicular steroidogenesis. J. Pharm. Exptl. Therap. 213: 228 (1980).
100. Greene, L. W., and Hollander, C. S. Sex and alcohol: the effects of alcohol on the hypothalamic-pituitary-gonadal axis. Alcoholism 4: 1 (1980).
101. Greene, M. H., Hoover, R. N., Eck, R. L., and Fraumeni, J. F. Cancer mortality among printing plant workers. Environ. Res. 20: 66 (1979).
102. Langård, S., Andersen, A., and Gylseth, B. Incidence of cancer among ferrochromium and ferrosilicon workers. Br. J. Ind. Med. 37: 114 (1980).
103. Axelsson, G., Rylander, R., and Schmidt, A. Mortality and incidence of tumors among ferrochromium workers. Brit. J. Ind. Med. 37: 121 (1980).
104. Lancaster, H. O. The mortality in Australia from cancers peculiar to the male. Med. J. Austral. 2: 41 (1952).
105. King, H., Diamond, E., and Lilienfeld, A. M. Some epidemiological aspects of cancer of the prostate. J. Chron. Dis. 16: 117 (1963).
106. Greenwald, P., Kirmss, V., and Burnett, W. S. Prostate cancer epidemiology: Widowerhood and cancer in spouses. J. Natl. Cancer Inst. 62: 1131 (1979).
107. Greenwald, P., Damm, A., Kirmiss, V., and Polan, A. K. Physical and demographic features of men before developing cancer of the prostate. J. Natl. Cancer Inst. 53: 341 (1974).
108. Rotkin, I. D. Studies in the epidemiology of prostatic cancer: Expanded sampling. Cancer Treat. Repts. 61: 173 (1977).
109. Schuman, L. M., Mandel, J., Blackard, C., Bauer, H., Scarlett, J., and McHugh, R. Epidemiologic study of prostatic cancer. Preliminary report. Cancer Treat. Repts. 61: 181 (1977).
110. Ernster, V. L., Sacks, S. T., Selvin, S., and Petrakis, N. L. Cancer incidence by marital status: U.S. Third National Cancer Survey. J. Natl. Cancer Inst. 63: 567 (1979).
111. Ernster, V. L., Selvin, S., Sacks, S. T., Austin, D. F., Brown, S. M., and Winkelstein, W. Prostatic cancer: Mortality and incidence rates by race and social class. Am. J. Epidemiol. 107: 311 (1978).
112. Ernster, V. L., Selvin, S., and Winkelstein, W. Cohort mortality for prostatic cancer among United States nonwhites. Science 200: 1165 (1978).
113. Hu, J. H., and White, J. E. Cancer incidence in the western United States: Ethnic differences. J. Natl. Med. Assoc. 71: 345 (1979).
114. Ross, R. K., McCurtis, J. W., Henderson, B. E., Menck, H. R., Mack, T. M., and Martin, S. P. Descriptive epidemiology of testicular and prostatic cancer in Los Angeles. Brit. J. Cancer 39: 284 (1979).
115. Blair, A., and Fraumeni, J. F. Geographic patterns of prostate cancer in the United States. J. Natl. Cancer Inst. 61: 1379 (1978).
116. Carroll, K. K. Experimental evidence of dietary factors and hormone-dependent cancers. Cancer Res. 35: 3374 (1975).
117. Hill, P., Wynder, E. L., Garbaczewski, L., Garnes, H., and Walker, A. R. P. Diet and urinary steroids in black and white North American men and black South African men. Cancer Res. 39: 5101 (1979).
118. Habib, F. K., Lee, I. R., Stitch, S. R., and Smith, P. H. Androgen levels in the plasma and prostatic tissues of patients with benign hypertrophy and carcinoma of the prostate. J. Endocrinol. 71: 99 (1976).
119. Geller, J., Albert, J., Loza, D., Gellers, S., Stoeltzing, W., and De La Vega, D. DHT concentrations in human prostate cancer tissue. J. Clin. Endocrinol. Metab. 46: 440 (1978).
120. Habib, F. K., and Stitch, S. R. The interrelationship of the metal and androgen binding proteins in normal and cancerous human prostatic itssues. Acta Endocrinol. Suppl. 199: 129 (1975).
121. Wallace, A. M., and Grant, J. K. Effect of zinc on androgen metabolism in the human hyperplastic prostate. Biochem. Soc. Trans. 3: 540 (1975).
122. Petering, H., Johnson, M. A., and Stemmer, K. L. Studies of zinc metabolism in the rat. I. Dose-response effects of cadmium. Arch. Environ. Health 23: 93 (1971).